The effect of pioglitazone on weight, lipid profile and liver enzymes in type 2 diabetic patients

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Abstract

Background: Pioglitazone is one of the antidiabetic agents used in the management of type 2 diabetes mellitus (DM). The effect of pioglitazone on blood glucose, lipid profile, liver enzymes and weight has been shown with conflicting results. In this study we aim to evaluate the effect of pioglitazone on the weight, lipid profile and liver enzymes in patients with DM.

Methods: In this single-arm clinical trial, 110 poorly controlled diabetic type 2 patients (63.6% female with mean age of 54.26 ± 8.96 years) who were on maximal dosage of metformin and glibenclamide were enrolled. Patients were treated with pioglitazone for 3 months and laboratory. Fasting blood sugar (FBS), haemoglobin A1C (HbA1C), cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), alkaline phosphatase (ALK-P), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and weight changes were measured before and at the end of the study.

Results: The levels of FBS ($p < 0.001$), HbA1c ($p < 0.001$), triglyceride ($p = 0.001$), ALT ($p = 0.005$) and ALK-P ($p = 0.001$) were significantly decreased, but weight was significantly increased ($p < 0.001$) after the intervention. There were no significant difference in cholesterol, LDL and HDL values before and after study.

Conclusion: Although pioglitazone causes a significant decrease in FBS, HbA1C and triglyceride levels, it is associated with weight gain, which would limit its utility.

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Keywords: lipid profile, liver enzyme, pioglitazone, type 2 diabetes mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by raised glucose levels which is associated with macrovascular and microvascular complications as well as dyslipidaemia, that increase morbidity and mortality [Erlich *et al.* 2013; Krauss, 2004]. There are various medications introduced to reduce glucose levels and improve DM patients' clinical status. Pioglitazone, a thiazolidinedione derivative, is an insulin-sensitizing agent developed for the treatment of T2DM [Zenari and Marangoni, 2013; Zou and Hu, 2013]. Pioglitazone is a peroxisome proliferator activated receptor-gamma (PPAR-γ) agonist which can reduce insulin resistance in liver, muscle and adipose tissue [Gross and Staels, 2007; Waugh *et al.* 2003; Zou and Hu, 2013] and improve glucose and lipid metabolism [Bajaj *et al.* 2004; Miyazaki *et al.* 2002].

Pioglitazone treatment in T2DM results in improving lipid profile including decrease in triglycerides and low-density lipoprotein (LDL), increase in high-density lipoprotein (HDL) and decrease in serum fatty acids [Aghamohammadzadeh *et al.* 2010; Chawla *et al.* 2013; Razavizade *et al.* 2013] as well as improved liver function tests [Belfort *et al.* 2006; Razavizade *et al.* 2013; Sanyal *et al.* 2010]. Unlike these findings, other studies were not able to demonstrate any significant improvement in liver function tests [Chawla *et al.* 2013] or lipid profile [You *et al.* 2010]. Unlike its beneficiary

effects, weight gain is one major side effect of this medication [Defronzo *et al.* 2013; Nafrialdi, 2012].

Previous reports indicate that compared with glibenclamide or metformin, pioglitazone alone or in combination with any of these agents could reduce blood glucose further [Ceriello *et al.* 2005]. However, there are controversies in reported effects of pioglitazone. So, it is important to define the exact role of pioglitazone on diabetes control, lipid profile, liver function and possible weight gain. In this study, we aim to evaluate the effect of pioglitazone in Iranian patients with T2DM.

Materials and methods

In this single-arm clinical trial, 110 patients aged 35–75 years with uncontrolled diabetes mellitus and no previous history of taking thiazolidinediones, who were on maximum dose of metformin (1.5–2 g) and glibenclamide (15–20 mg) for at least 1 month, having HbA1c 7.5–11% and fasting blood sugar (FBS) ⩾140 mg/dl were enrolled. Patients with significant renal, cardiac, liver, lung, or neurological disease, anaemia, systemic glucocorticoid therapy patients receiving β-blockers, prior use of or known allergy to any type of available thiazolidinediones, patients currently pregnant, breastfeeding, smokers, and subjects who abused alcohol or drugs and those with a body mass index (BMI) greater than 40 kg/m^2 were excluded from this study. Subjects were also excluded if they had been treated with insulin or had started treatment with a statin or any fibric acid derivative within 2 months of the beginning of the study. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and written informed consent was obtained from all patients.

All patients underwent a complete laboratory survey including FBS, lipid profile including cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL), alkaline phosphatase (ALK-P), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and the weight of patients were assessed at the time of laboratory survey. Then the pioglitazone at a dose of 30 mg was added to the treatment protocol of all patients and they were followed up for 3 months. All above-mentioned laboratory investigations and weight assessing were repeated after 3 months and the obtained data before and after therapeutic intervention were studied.

Data analysis

All data were analysed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, Illinois). Baseline data are reported as mean ± standard deviation (continuous data) or percentages (categorical data), depending on the data level. To compare the results before and after the intervention, paired t test was used for statistical analysis. A p value of 0.05 or less was considered significant.

Results

In this study, 110 patients with type 2 DM including 70 (63.6%) females and 40 (36.4%) males with a mean age of 54.26 ± 8.96 years were studied.

Table 1 shows the laboratory findings before and after the intervention. As the table shows FBS, HbA1c, TG, ALT, ALK-P were significantly decreased and patients' weight was increased following intervention. However, no significant differences were observed in the level of cholesterol, HDL, LDL and AST before and after the intervention. Mean percentage of increase in weight was 1.07 ± 0.29%.

Discussion

In this study, we evaluated the effect of adding pioglitazone to T2DM patients' treatment protocol which showed significant improvement in FBS and HbA1c as well as triglyceride and ALT levels. The consistent decrease of blood glucose and HbA1C indicates the efficacy of pioglitazone in controlling glycaemia.

Similar findings were found in our previous study about the effects of pioglitazone in T2DM patients [Aghamohammadzadeh *et al.* 2010]. Improvement in glycaemia control following pioglitazone use had been demonstrated previously [Al-Azzam *et al.* 2012; Lee *et al.* 2013; Nafrialdi, 2012; You *et al.* 2010]. It is reported that pioglitazone causes a reduction in insulin resistance and reduces fasting plasma insulin levels that will result in improved glycaemia control [Pavo *et al.* 2003].

In patients with type 2 diabetes, there is a strong association between high triglyceride and low HDL levels and cardiovascular morbidity and mortality [Pfützner *et al.* 2011]. We also observed that pioglitazone caused significant reduction in triglyceride levels, but has no significant effect on cholesterol, HDL and LDL. Previous studies have shown significant reduction in triglyceride as

Table 1. Demographic and anthropometric findings between groups.

Variable	Before intervention	After intervention	*p* value
FBS (mg/dl)	221.01±46.61	146.24±46.61	<0.001
HbA1C (%)	8.51±1.54	7.29±0.90	<0.001
Cholesterol (mg/dl)	156.93±27.16	155.55±29.26	0.61
Triglyceride (mg/dl)	165.15±72.35	145.83±67.19	<0.001
LDL (mg/dl)	80.38±23.19	82.28±23.35	0.42
HDL (mg/dl)	43.60±10.19	44.39±9.77	0.34
AST (IU/ml)	21.49±8.65	21.45±8.16	0.95
ALT (IU/ml)	26.74±13.19	23.66±12.29	<0.005
ALK-P (IU/L)	190.41±63.29	173.62±57.05	<0.001
Weight (kg)	76.78±11.40	77.60±11.79	0.000

FBS, fasting blood sugar; HbA1C, haemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

well as increase in HDL, but the changes in LDL and cholesterol levels were not significant [Aghamohammadzadeh *et al.* 2010; Chawla *et al.* 2013; Razavizade *et al.* 2013]. Unlike these findings, You and colleagues found significant decrease in total cholesterol and LDL levels, but the decrease in triglyceride and HDL levels were not significant [You *et al.* 2010]. This difference may be due to the longer duration of drug treatment in different studies as well as medication doses, patients' heterogeneity (considering weight, gender, daily physical activity).

It is shown that pioglitazone can prevent inflammatory process and in result, improve liver function [Razavizade *et al.* 2013; Sanyal *et al.* 2010]. Sanyal and colleagues showed that the consumption of pioglitazone compared with placebo significantly reduced the serum levels of AST and ALT [Sanyal *et al.* 2010]. Belfort and colleagues also observed significant reduction in AST and ALT levels following pioglitazone therapy in patients with nonalcoholic steatohepatitis [Belfort *et al.* 2006]. In our study, we observed significant reduction in ALT and ALK-P, but no changes were seen in AST levels indicating that pioglitazone is not harmful for the liver. However, Chawla and colleagues observed no improvement in liver function test [Chawla *et al.* 2013]. We suggest that the differences in the results might be due to the variations in the studies duration, patients' characteristics and medication dosage. However, the existence of controversy in their effect on ALT and AST levels are the main concerns that need complementary investigations.

ALT and AST serve as a marker of hepatocyte injury. Chronic mild elevation of these transaminases is frequently found in type 2 diabetic patients. Loss of insulin effect on the liver leads to glycogenolysis and an increase in hepatic glucose production. Abnormalities of triglyceride storage and lipolysis in insulin-sensitive tissues such as the liver are an early manifestation of conditions characterized by insulin resistance and are detectable earlier than fasting hyperglycaemia. Insulin resistance is proposed to lead to fatty changes in the liver. The excess in free fatty acids found in the insulin-resistant state is known to be directly toxic to hepatocytes and thus increasing ALT and AST. Also, proinflammatory cytokines are increased during insulin-resistant state which also contributes to hepatocellular injury [Grove *et al.* 1997; Neuschwander-Tetri and Caldwell, 2003]. It is possible that thiazolidinediones including pioglitazone improve the liver function tests by their role in improving in insulin sensitivity and their anti-inflammatory effects [Browning and Horton, 2004].

Weight gain is a major problem that limits pioglitazone use [Chawla *et al.* 2013; Sanyal *et al.* 2010]. Similar to previous findings [Chawla *et al.* 2013; Nafrialdi, 2012; Sanyal *et al.* 2010], we observed significant increase in patients' weight following pioglitazone use. However, this increase was only 1.07%. Some previous studies have reported an increase of 5% in body weight after pioglitazone use [Chawla *et al.* 2013; Nafrialdi, 2012; Sanyal *et al.* 2010]; however, similar to our findings, Pavo and colleagues found lower weight increase (0.9%) following pioglitazone use [Pavo *et al.* 2003]. Unlike all of these findings, You and colleagues did not find weight gain following pioglitazone use [You *et al.* 2010]. It is believed that increased body weight is due to water retention and fat accumulation [Derosa, 2010; Pendsey

et al. 2002; Yki-Järvinen, 2004]. Although many studies have shown that pioglitazone may cause weight gain but some of them demonstrated that a proper diet may prevent this side effect in diabetic patients taking pioglitazone for more than 16 weeks [Ditschuneit, 2006]. Also, Fonseca in his study showed that pioglitazone may cause weight gain but adherence to a proper diet can attenuate this effect [Fonseca, 2003].

Although pioglitazone improved glucose and reduced HbA1c in diabetic patients, but could not fully improve the lipid profile and it was associated with weight gain. Therefore, other therapeutic interventions such as a proportional weight loss control diet must be accompanied with this therapeutic intervention in order to optimize the effectiveness of these drugs.

It is reported that different ethnicities in different regions have different outcome and response to the same endocrine disease despite similar or even lower incidence of the disorder [Golden *et al.* 2012], so the treatment protocol, the dosage of treatment used and the observed outcome varies between different ethnicities. It is also shown that even various ethnicities in a same geographical region demonstrate different symptoms and outcome [Chong *et al.* 2009]. Previous studies have also shown that each ethnicity and racial group differs in severity of the insulin resistance [Spanakis and Golden, 2013]. So, it is possible that the observed effects of pioglitazone in our study which are different from other studies could be due to racial and ethnical differences between studies. It should be noted that the observed results are among the patients with T2DM in Iran and it is possible that the observed differences, especially in lipid profile, could be due to this.

Limitations

This study had some limitations. We did not have a control group, so could not exactly compare the changes observed in lipid profile, glycaemia control, liver function and weight gain, as it is possible that some of these changes occur even without pioglitazone use. We did not evaluate patients' physical activity which limits the findings on weight gain. We also did not put patients on a similar diet. This may be another limitation, as the diet used has significant effects on the evaluated variables. Most studies have treated patients for longer time (more than 40 weeks) and evaluated the long-term use of pioglitazone; the short period of treatment and follow up in our study is another limitation. However, we performed the study to show early beneficiary results of pioglitazone treatment.

Conclusion

It is concluded that pioglitazone is a good antidiabetic agent in patients with T2DM who do not respond properly to maximum dose of glibenclamide and metformin. This agent has no negative impact on lipid profile and liver function tests but carries a trivial risk of weight gain which would limit its utility.

Conflict of interest statement

The authors have no conflicts of interest to report.

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References

Aghamohammadzadeh, N., Tabrizi, A. and Niafar, M. (2010) Efficacy of adding glutazone to the maximum dose of glibenclamide and metformin resistant on type 2 diabetic patients. *Casp J Intern Med* 1: 9–11.

Al-Azzam, S., Alomari, M., Khader, Y., Almahasneh, F., Muflih, S. and Altawalbeh, S. (2012) Effects of pioglitazone add-on to gliclazide and metformin on glycemic control in patients with type 2 diabetes. *Endocr Res* 37: 7–11.

Bajaj, M., Suraamornkul, S., Piper, P., Hardies, L., Glass, L., Cersosimo, E. *et al.* (2004) Decreased plasma adiponectin concentrations are closely related to hepatic fat content and hepatic insulin resistance in pioglitazone-treated type 2 diabetic patients. *J Clin Endocrinol Metab* 89: 200–206.

Belfort, R., Harrison, S., Brown, K., Darland, C., Finch, J., Hardies, J. *et al.* (2006) A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N Engl J Med* 355: 2297–2307.

Browning, J. and Horton, J. (2004) Molecular mediators of hepatic steatosis and liver injury. *J Clin Invest* 114: 147–152.

Ceriello, A., Johns, D., Widel, M., Eckland, D., Gilmore, K. and Tan, M. (2005) Comparison of effect of pioglitazone with metformin or sulfonylurea (monotherapy and combination therapy) on postload glycemia and composite insulin sensitivity index during an oral glucose tolerance test in patients with type 2 diabetes. *Diabetes Care* 28: 266–272.

Chawla, S., Kaushik, N., Singh, N., Ghosh, R. and Saxena, A. (2013) Effect of addition of either sitagliptin or pioglitazone in patients with uncontrolled type 2 diabetes mellitus on metformin: A randomized controlled trial. *J Pharmacol Pharmacother* 4: 27–32.

Chong, S., Subramaniam, M., Chan, Y., Chua, H., Liow, P., Pek, E. *et al.* (2009) Depressive symptoms and diabetes mellitus in an Asian multiracial population. *Asian J Psychiatr* 2: 66–70.

Defronzo, R., Mehta, R. and Schnure, J. (2013) Pleiotropic effects of thiazolidinediones: implications for the treatment of patients with type 2 diabetes mellitus. *Hosp Pract (1995)* 41: 132–147.

Derosa, G. (2010) Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus: Comparison with other oral antihyperglycaemic agents. *Drugs* 70: 1945–1961.

Ditschuneit, H. (2006) Do meal replacement drinks have a role in diabetes management? *Nestle Nutr Workshop Ser Clin Perform Programme* 11: 171–179.

Erlich, D., Slawson, D. and Shaughnessy, A. (2013) Diabetes update: new drugs to manage type 2 diabetes. *FP Essent* 408: 20–24.

Fonseca, V. (2003) Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *A J Med* 115: 42S–48S.

Golden, S., Brown, A., Cauley, J., Chin, M., Gary-Webb, T., Kim, C. *et al.* (2012) Health disparities in endocrine disorders: biological, clinical, and nonclinical factors - an Endocrine Society scientific statement. *J Clin Endocrinol Metab* 97: E1579-E1639.

Gross, B. and Staels, B. (2007) PPAR agonists: multimodal drugs for the treatment of type-2 diabetes. *Best Pract Res Clin Endocrinol Metab* 21: 687–710.

Grove, J., Daly, A., Bassendine, M. and Day, C. (1997) Association of a tumor necrosis factor promoter polymorphism with susceptibility to alcoholic steatohepatitis. *Hepatology* 26: 143–146.

Krauss, R. (2004) Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care* 27: 1496–1504.

Lee, Y., Song, S., Kim, K., Cho, Y., Choi, Y., Yun, Y. *et al.* (2013) Glycemic effectiveness of metformin-based dual-combination therapies with sulphonylurea, pioglitazone, or DPP4-inhibitor in drug-naïve Korean type 2 diabetic patients. *Diabetes Metab J* 37: 465–474.

Miyazaki, Y., Mahankali, A., Matsuda, M., Mahankali, S., Hardies, J., Cusi, K. *et al.* (2002) Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. *J Clin Endocrinol Metab* 87: 2784–2791.

Nafrialdi. (2012) Efficacy and safety of pioglitazone in type 2 diabetes mellitus: a postmarketing observational study. *Acta Med Indones* 44: 28–34.

Neuschwander-Tetri, B. and Caldwell, S. (2003) Nonalcoholic steatohepatitis: summary of AASLD single topic conference. *Hepatology* 37: 1202–1219.

Pavo, I., Jermendy, G., Varkonyi, T., Kerenyi, Z., Gyimesi, A., Shoustov, S. *et al.* (2003) Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type 2 diabetes. *J Clin Endocrinol Metab* 88: 1637–1645.

Pendsey, S., Dhanvijay, V. and Joshi, P. (2002) Efficacy of pioglitazone as an add on drug with insulin, glibenclamide and metformin in patients with uncontrolled type 2 diabetes mellitus. *Diabetologia Croatia* 31: 51–57.

Pfützner, A., Schöndorf, T., Tschöpe, D., Lobmann, R., Merke, J., Müller, J. *et al.* (2011) PIOfix-Study: Effects of pioglitazone/metformin fixed combination in comparison with a combination of metformin with glimepiride on diabetic dyslipidemia. *Diabetes Technol Ther* 13: 637-643.

Razavizade, M., Jamali, R., Arj, A., Matini, S., Moraveji, A. and Taherkhani, E. (2013) The effect of pioglitazone and metformin on liver function tests, insulin resistance, and liver fat content in nonalcoholic Fatty liver disease: a randomized double blinded clinical trial. *Hepat Mon* 13: e9270.

Sanyal, A., Chalasani, N., Kowdley, K., McCullough, A., Diehl, A., Bass, N. *et al.* (2010) Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med* 362: 1675–1685.

Spanakis, E. and Golden, S. (2013) Race/ethnic difference in diabetes and diabetic complications. *Curr Diab Rep* 13: 814–823.

You, S., Kim, B., Hong, S., Ahn, C. and Lim, D. (2010) The effects of pioglitazone in reducing atherosclerosis progression and neointima volume in type 2 diabetic patients: prospective randomized study with volumetric intravascular ultrasonography analysis. *Korean Circ J* 40: 625–631.

Yki-Järvinen, H. (2004) Thiazolidinediones. *N Engl J Med* 351: 1106–1118.

Waugh, J., Keating, G., Plosker, G., Easthope, S. and Robinson, D. (2003) Pioglitazone: A review of its use in Type 2 diabetes mellitus. *Drugs* 66: 340–341.

Zenari, L. and Marangoni, A. (2013) What are the preferred strategies for control of glycaemic variability in patients with type 2 diabetes mellitus? *Diabetes Obes Metab* 15(Suppl. 2): 17–25.

Zou, C. and Hu, H. (2013) Use of pioglitazone in the treatment of diabetes: effect on cardiovascular risk. *Vasc Health Risk Manag* 9: 429–433.